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Guidance for Industry

Submitting a Notice of Claimed Investigational Exemption in Electronic Format to the Center for Veterinary Medicine via E-Mail

This guidance document is intended to instruct those participating in the Center for Veterinary Medicine's submission of Notices of Claimed Investigational Exemption (NCIEs) in electronic format via e-mail.

This guidance represents the Center's current thinking on submitting a NCIEs in electronic format via e-mail and updates the Guidance for Industry #59 dated June 16, 1997. It does not create or confer any rights for or on any person and does not bind FDA or the public.

An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulation, or both. If a regulated company or person wishes or chooses to use an approach other than that set forth in this guidance document, the Center will, upon request, discuss with that company or person alternative methods of complying with the applicable statutes and regulations. The Center encourages industry to discuss alternative approaches with the Center before implementing them to avoid unnecessary or wasteful expenditures of resources.

Comments and suggestions regarding this document should be submitted, via paper, to the Policy and Regulations Team, Center for Veterinary Medicine, HFV-6, 7500 Standish Place, Rockville, MD 20855.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
January 1999

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GUIDANCE FOR INDUSTRY[1]

SUBMITTING A NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION IN ELECTRONIC FORMAT TO THE CENTER FOR VETERINARY MEDICINE VIA E-MAIL

I. BACKGROUND

To determine the practicality of electronic submission and review as an alternative to the current paper-based processes, CVM initiated a pilot project that allowed sponsor companies to submit Notices of Claimed Investigational Exemption (NCIEs), often referred to as drug shipment notices, as e-mail attachments via the Internet.[2] NCIEs were selected for the initial pilot because of their simplicity, size, and broad use within CVM and by nearly all sponsors. (See Appendix 1 for specifications and general instructions on submitting information electronically to CVM via e-mail.)

The pilot began on September 8, 1997, and was conducted for six months, ending on March 9, 1998, with an interim review after three months, on December 8, 1997. The Three Month Report[3] recommended that the Center "officially adopt the procedures and finalize the guidance document for NCIE electronic submissions."

The NCIE electronic submission pilot project was therefore extended for a one year period, beginning on March 10, 1998 and ending on March 10, 1999, to allow for finalization of procedures. This current guidance document is based on the Center and participating animal drug industry's experiences in the pilot project and incorporates those procedures into NCIEs electronic submission. It presents the procedures necessary for electronic NCIEs submitted to the Center to be accepted as the official original document.

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[1] This guidance has been prepared by the Center for Veterinary Medicine (CVM) at the Food and Drug Administration. For additional copies of this guidance, access the document on the WWW by connecting to the CVM Home Page at http://www.fda.gov/cvm or send a request to the Communications Staff, HFV-12, 7500 Standish Place, Rockville, MD 20855.

[2] Please note that a **new** investigational file must be established in accordance with current practices, and not by use of the electronic NCIE.

[3] A copy of the Three Month Report can be found on the CVM Home Page at http://www.fda.gov/cvm.

II. REQUIREMENTS TO PARTICIPATE

The requirements set forth in this guidance document are dependent on CVM's current information technology capability and its ability to ensure the confidentiality, integrity, security and authentication of data submitted to the Center in electronic format via e-mail.

For the purposes of submitting electronic NCIEs, the sponsor agrees to use the NCIE form provided by CVM (FORM FDA 3458 (For use with electronic submissions)[4] OMB No. 0910-0117), which will be submitted to CVM as an Adobe® PDF file (created in Adobe Acrobat® Exchange® compatible with Adobe® version 3.0).[5] The sponsor must be able to either create a word processing document with the necessary data and convert it to a PDF file, or alternatively to enter the data into an Adobe Acrobat form directly.

The NCIEs may be submitted for review by any of the following CVM divisions: Division of Therapeutic Drugs for Non-Food Animals (HFV-110), Division of Biometrics and Production Drugs (HFV-120), Division of Therapeutic Drugs for Food Animals (HFV-130), and Division of Animal Feeds (HFV-220).

The NCIEs will be submitted via an Internet e-mail message from the sponsor to CVM. For reasons of security and verifying the sender's identity, the sponsor will register each individual participant with the Center as outlined in Appendix 1. This includes a sponsor coordinator and all individual contacts that will be sending submissions via e-mail.

The sponsor must agree to attach the NCIE as a PDF file to the e-mail message. Only one PDF attachment per e-mail message will be permitted. The maximum file size for submitting information electronically via e-mail is 1 Megabyte (1 MB). No information should be included in the body of the e-mail message.

The sponsor must agree to use a standardized convention for the subject line of each e-mail transmission. The sponsor will type in the four characters, **NCIE**, in capital letters, no quotation marks, and no other words in the subject line.

These requirements must be met for CVM to accept NCIEs electronically as the official copy, in lieu of paper, as allowed by 21 CFR 11. If sponsors are not capable of meeting these requirements, then they must submit the NCIEs in paper.

[4] A copy of the form along with instructions for completing it can be found on the CVM Home Page, http://www.fda.gov/cvm.

[5] FDA use of specific products does not constitute an endorsement of those products.

III. NCIE REGULATORY COMPLIANCE

Typically, time-sensitive information is submitted via certified mail so that the sponsor has a record verifying the date and name of individual who received the information at CVM. This also provides a legal basis by which sponsors can assert their compliance with laws and regulations.

For NCIEs, sponsors are required to submit their drug shipment notices ***prior*** to the shipment of investigational new animal drugs and food additives for use in clinical animals as required by 21 CFR 511.1(b)(4) and 21 CFR 570.17 respecitively. Currently, CVM reviews the date on the cover letter of paper NCIE to determine whether notification was made prior to delivery. For an electronic NCIE, the date field entered by the sponsor within the form will serve as the date of notification to CVM. As a means of verifying that the information was received, CVM should respond with an e-mail message back to the sponsor within two business days of receipt of the electronic NCIE.

IV. ERROR REPORTING AND EVALUATION

For purposes of the NCIE electronic submission project, sponsors need only report to CVM exceptions to normal processing at the time they occur. An example of an exception would be not receiving an acknowledgment from CVM within two business days (see Appendix 1 for details). If an electronic acknowledgment has not been received from CVM by the third business day after the sponsor sent the electronic submission, the sponsor should contact CVM. Any such problems or errors should be reported by telephone to CVM's Electronic Document Control Unit (301-827-8277).

Direct all other comments, questions on the instructions, and suggestions for future electronic submission projects to either of the Project Coordinators,
Dr. Charles Andres (301-827-7561) or Ms. E. L. Parbuoni (301-827-7562).

These comments will help determine the future direction for electronic submissions within the Center. CVM will continue to monitor and evaluate electronic submission initiatives and make recommendations for improvement which will be incorporated into future guidance documents.

V. CHECKLIST FOR NCIE PROCESS USING WORD PROCESSING FORM

This checklist describes a process for creating a PDF file using a word processing form and printing it to the Acrobat PDFWriter. The PDF file may be created by other means.

1. Open blank NCIE form in word processing package.
2. Make sure Acrobat PDFWriter is selected as the default printer.
3. Fill in all pertinent sections of NCIE.
4. Print the word processing document to Acrobat PDFWriter to create a PDF file.
5. Name the PDF file according to established naming conventions. (Must use the 8.3 file naming convention) Save the PDF file in the appropriate directory location and close it.
6. Open the PDF file in Adobe Acrobat Exchange, select "Save As" and select the "Security" options for "Specify Password To: Open the Document". Enter your password and click OK. Verify the password by entering it again and then "Save" the PDF file.
7. Open e-mail and begin a new message.
8. Address it to **cvmdcu@bangate.fda.gov.**
9. Type **NCIE** in the subject line, all capital letters, no other punctuation or information.
10. Do not type anything in the body of the message.
11. Attach the PDF file of the NCIE to the e-mail message.
12. Send the e-mail message.
13. If you do not receive an acknowledgment receipt from CVM (stars@bangate.fda.gov) by the third business day after you have sent the submission, call the Electronic Document Control Unit at 301-827-8277 to report the problem and find out what happened to your submission.

VI. NCIE FORM

A copy of the NCIE form, FORM FDA 3458 (For use with electronic submissions), is available on the CVM Home Page at http://www.fda.gov/cvm/.

Appendix 1

How to Submit Information Electronically via E-mail

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HOW TO SUBMIT INFORMATION ELECTRONICALLY VIA E-MAIL

I. OVERVIEW

Since the publication of FDA's Final Rule on Electronic Records and Signatures (21 CFR Part 11) on March 20, 1997, the Center for Veterinary Medicine (CVM) has taken advantage of the opportunity to accept electronic submissions of certain information in lieu of paper. These regulations require that the Agency identify in public docket No. 92S-0251 the type, format, and procedures acceptable for official electronic submissions.

CVM is detailing the type and format of electronic information that it accepts in specific guidance documents for industry that are listed in the public docket. In addition, CVM has adopted standard procedures for submission of these official electronic submissions of information to the Center via e-mail. These procedures are detailed in this appendix and are based on the current information technology capabilities of the Center and the requirements of the Electronic Records and Signature regulation.

II. ROLES OF PARTIES INVOLVED

Successful electronic submission of information for review and evaluation via e-mail requires a successful partnership between CVM and regulated industry. Information needs to be exchanged and errors need to be resolved. The roles and responsibilities of key parties involved in electronic submission projects are outlined below. Since persons assigned to these roles may vary depending on the specific electronic submission, CVM's contact names are provided in submission specific guidance that are found on the CVM Home Page at http://www.fda.gov/cvm.

A. CVM Project Roles and Responsibilities

Role	Responsibilities
Project Coordinator	Facilitate communication within CVM, and oversee the coordination of electronic submissions.
CVM Electronic Submission Working Group	Provide specifications necessary for the use and processing of electronic submissions. Gather information on the current processing of paper submissions, and assist in design of electronic processing procedures. Evaluate the success of electronic submission on the efficiency of the review process.
Technical Specialist	Confirm electronic format used and security required for transmission of electronic information are compatible with current CVM LAN configuration. Assess future needs for electronic storage and retrieval of information, and recommend any needed additional capability. Coordinate LAN capabilities for support of the electronic submissions. Also responsible for compliance with Agency Initiatives and Standards.
Processing Specialist	Coordinate actual processing, logging, tracking, and storage of electronically submitted and stored submissions. Recommend changes to existing tracking system, and responsible for compatibility of overall system (integration of paper and electronic submissions).
Electronic Document Control Unit (e-CVMDCU)	Receive, log, process, and file electronic submissions. E-mail address is cvmdcu@bangate.fda.gov and voice-mail phone number is 301-827-8277

B. CVM Pivotal Roles And Summary Of Primary Duties

Project Coordinator

- Coordinate project within the Center and between the industry and the Center.
- Inform Office and Center Management of progress of electronic submissions projects.

Technical Specialist

- Develop electronic format in conjunction with industry representatives to be compatible for LAN capabilities of CVM.
- Develop security measures to safeguard CVM LAN and confidentiality of received or transmitted information.
- Develop filing system for electronic submissions.
- Develop LAN requirements and identify any additional electronic capabilities.
- Evaluate CVM's Federal Managers Financial Integrity Act requirements for submission archiving and oversees implementation of such plan.
- Liaison with Agency Initiatives and Standards.
- Present training to industry participants.

Processing Specialist

- Develop processes for receipt, logging, tracking, and filing of electronically formatted submissions.
- Present training to ONADE Reviewers.
- Prepare Standard Operating Procedures (SOPs)
- Train Document Control Unit (DCU).
- Prepare reports for monitoring electronic submission progress.
- Compile and prepare statistics at completion of each project.

CVM Review Team Representatives

- Assist in developing the electronic format to be used for each electronic submission type.
- Provide assistance to reviewers within their respective teams.
- Recommend processing procedures for electronic submissions.
- Design training program for reviewers.
- Provide evaluation during and at the end of the electronic submission pilots, including suggestions for changes, modifications and future direction of electronic submissions within the Center.

e-CVMDCU

- Log submissions on a daily basis, route submissions to review organization, and complete STARS tracking record.
- File review copy of the electronic submission.
- Route any necessary copies within the Center.
- Send receipt to originating Sponsor Contact.
- Complete tracking and administrative record for submissions.
- Maintain SOPs for receipt logging, tracking, and filing of submissions.

C. Sponsor Project Roles and Responsibilities

Role	Responsibilities
Sponsor Project Coordinator	Coordinate project within the sponsor company and between the sponsor and CVM. Confirm electronic format to be used and the security required for transmission of electronic submissions are compatible with the sponsor's computer configuration. Assess needs for electronic storage and retrieval of information, and recommend any needed capabilities. Coordinate internal process capabilities for support of electronic submissions. Also responsible for compliance with 21 CFR 11.
Sponsor Contacts	Process, prepare and file electronically submitted information and ensure appropriate filing of the electronic submission. Receive confirmation of successful transmission from e-CVMDCU. Report pertinent project information to the Sponsor Project Coordinator.

D. Sponsor Pivotal Roles And Summary Of Primary Duties

Sponsor Project Coordinator

- Coordinate electronic submissions between the sponsor and CVM.
- Ensure security measures to safeguard computer system and confidentiality of information transmitted and received. Address internal security concerns (virus, etc.).
- Present training to person(s) preparing electronic submissions.
- Develop filing system for electronic submissions. Address computer system requirements and identify any needed capabilities.
- Ensure adherence to timelines.
- Evaluate requirements for electronic file records and oversee implementation of such plan in compliance with 21 CFR 11.
- Develop processes for receipt, logging, tracking, and filing of electronic submissions.
- Prepare flow chart for internal processing of electronic submissions.
- Prepare SOPs and user documentation.
- Prepare reports for monitoring electronic submission process.
- Monitor the progress of electronic submission projects.
- Maintain sponsor password to open CVM correspondence.

Sponsor Contacts

- Create electronic submissions and transmit PDF copy to e-CVMDCU.
- Retain electronic submission in accordance with internal procedures.
- Forward any necessary information on the electronic submission processing to the Sponsor Project Coordinator.
- Process confirmation from e-CVMDCU.
- Report problems as they occur to e-CVMDCU at 301-827-8277.
- Maintain personal password for encryption of PDF file to CVM.

III. REGISTRATION TO SUBMIT ELECTRONIC SUBMISSIONS LISTED IN ELECTRONIC SUBMISSIONS DOCKET 92S-0251.

To participate in CVM's electronic submissions via e-mail, the sponsor must provide certain certification as required in 21 CFR 11.100. In addition to the certification to the Agency's Office of Regional Operations that the electronic signature is the legally binding equivalent of the signer's handwritten signature, CVM needs other information to ensure the confidentiality, integrity, security and authentication of data submitted to the Center in electronic format via e-mail.

Sponsors wishing to provide regulatory submissions in electronic format to CVM via e-mail need only register once to participate in any or all projects listed in the Electronic Submission Docket 92S-0251.

A. Sponsor Paper Registration and Sponsor Password

Sponsors wishing to register must send a single, original, signed Registration Letter to CVM, as well as an identical electronic copy (via e-mail to cvmdcu@bangate.fda.gov), in order to be eligible to participate in electronic submissions. In this letter, the sponsor shall identify:

1. name, mailing address, phone number, and e-mail address of the Sponsor Project Coordinator;
2. name, mailing address, phone number, and e-mail address for each contact person who will be submitting electronic submissions;
3. password used by the sponsor to encrypt the electronic Registration Letter submitted via e-mail. This same password will be used by CVM to encrypt future receipts sent to all contacts acknowledging each electronic submission submitted and processed for that sponsor; and
4. the subject of letter will be **Registration Letter for Electronic Submission to CVM** to clearly identify the purpose of the letter.

CVM will check for sponsor password duplication (same sponsor password for different sponsors). If duplicate passwords exist between sponsors, CVM will contact each Sponsor Project Coordinator and request that new passwords be selected. The Center should acknowledge the acceptance of the sponsor as an electronic submission participant in a paper letter.

Example of Registration Letter

Ms. Elizabeth L. Parbuoni
Office of New Animal Drug Evaluation
Center for Veterinary Medicine
7500 Standish Place (HFV-100)
Rockville, Maryland 20855

Subject: Registration Letter for Electronic Submission to CVM

Dear Ms. Parbuoni:

This letter notifies the Center for Veterinary Medicine (CVM) of our intent to submit information via e-mail as permitted under 92S-0251 (Electronic Submissions Docket). An attachment to this Registration Letter contains the name of the person who will serve as our Sponsor Project Coordinator and the names of our contact persons who will be submitting electronic information, along with their mailing addresses, phone numbers, and e-mail addresses. We also have identified a password to be used by CVM for encrypting all receipts back to us.

We certify to the Agency that the electronic signatures (e-mail address and individual passwords) used by our Sponsor Contacts and Sponsor Project Coordinator are intended to be the legally binding equivalent of traditional handwritten signatures.

We are submitting an electronic copy of this request to cvmdcu@bangate.fda.gov encrypted with our password.

After acknowledgment from the Center, each of our contact people will separately send via e-mail an encrypted file containing his/her individual password.

We look forward to receipt of CVM's letter acknowledging our intent to submit electronic information via e-mail and our acceptance into the Electronic Submission Project.

Sincerely yours,

B. Sponsor Contact Electronic Registration and Individual Passwords

CVM will decrypt the electronic Registration Letter with the sponsor password identified in the paper copy of the Registration Letter. After CVM successfully accesses the electronic Registration Letter, the Center will generate an electronic receipt for the Registration Letter and send back, via e-mail, to the Sponsor Project Coordinator as a encrypted PDF file. This electronic receipt is a courtesy acknowledgment that the electronic Registration Letter was received and was accessible.

Upon receipt of CVM's acknowledgment and paper acceptance letter, the Sponsor Project Coordinator will notify CVM of his or her personal password and instruct each Sponsor Contact to do the same. This will be done via an e-mail message. The subject line of this e-mail message will be **PASSWORD**. This e-mail message will have a PDF attachment encrypted with the sponsor password (from the paper Registration Letter). The encrypted PDF attachment will contain the new personal password to be used for that person's future submissions. The new password may not be used until the sponsor has received an acknowledgment receipt, via e-mail, from CVM. Individual passwords should be changed after an appropriate period of time to assure security. CVM will monitor the aging of passwords and require re-initialization at minimum periods. Changes to passwords follow the same process used to establish the initial password.

C. Changes to the Sponsor Registration

Conditions of the electronic submissions project registration may be changed on request of the Sponsor Project Coordinator. These changes may include, but are not limited to, adding or removing a Sponsor Contact, adding or removing a Sponsor Project Coordinator, change of the sponsor password, changes to e-mail addresses, changes to sponsor names, etc. This does not include any individual password changes. See Section III.B of this appendix for changes to individual password.

To request a change, the Sponsor Project Coordinator sends an e-mail message to e-CVMDCU with the subject line of **CHANGE**. The e-mail message will have a PDF file attached that has been encrypted by the Sponsor Project Coordinator password. The PDF file attached will contain the specified change(s) to be made.

IV. PROCESSING PROCEDURES FOR ELECTRONIC SUBMISSIONS

Information transmitted to CVM via e-mail for each electronic submission must adhere to minimum standards to ensure the confidentiality, integrity, security and authentication. CVM can process only submissions that comply with the Electronic Records and Electronic Signatures final rule. Requirements that are published in the Agency Electronic Docket (92S-0251) take into consideration the current information technology capabilities of CVM. Adherence to these standards is verified by the Center's e-mail processing, and only submissions in full compliance can be successfully processed as electronic submissions.

Each electronic submission is transmitted as an Adobe® PDF file (created in Adobe Acrobat® Exchange® compatible with version 3.0)[1] attached to an e-mail. Each e-mail with the attached submission is sent to the e-CVMDCU at cvmdcu@bangate.fda.gov. Submissions are acknowledged with a receipt issued within two working days from CVM's Submission Tracking and Reporting System (STARS) account at stars@bangate.fda.gov confirming the submission was successfully processed.

A. Gateway and Communication Requirements

The configuration of a sponsor's e-mail software or Internet gateway is critical to the successful interchange of electronic information with the CVM over the Internet. Electronic mail formats are not completely standardized; however, most gateways can be configured to accommodate the more recent and reliable formats. Many gateways limit the size of attachments allowed; therefore, for the purpose of interchange with the CVM, the attachment size must be limited to no more than 1 Megabyte (1 MB).

Basic requirements for sending e-mail with an attachment to the CVM will require MIME type e-mail encoding of the level that allows 8-bit or binary attachments. The technical specifications described within this section may be used to troubleshoot e-mail problems.

The sponsor's e-mail software or Internet gateway must be configured to generate "MIME-Version: 1.0" in the header field and recognize the Content-Transfer-Encoding header field in the e-mail message. It must be able to decode all received data encoded by either quoted-printable or Base64 implementation and be able to encode and label 8-bit or binary data using a Content-Transfer-Encoding type of either quoted-printable or Base64 as appropriate. This will allow attached, password-encrypted PDF files to be transmitted as part of the transmission package.

[1] FDA use of specific products does not constitute an endorsement of that product

Sponsor's e-mail software or Internet gateway must explicitly handle the following media type values:

Text:

- It must recognize and display "text" mail with the character set US-ASCII.
- It must recognize other character sets at least to the extent of being able to inform the user about what character set the message uses.
- It must recognize the ISO-8859 character sets to the extent of being able to display those characters that are common to the ISO-8859 and US-ASCII, namely all characters represented by octet values 1-127.

Multi-part and application:

- It must at a minimum provide facilities to treat any unrecognized subtypes as if they were "application/octet-stream".
- It must offer the ability to remove either of the quoted-printable or Base64 encoding defined in this document if they were used and put the resulting information in a user file.
- It must recognize a mixed subtype and display all relevant information on the message level and the body part header level and then display or offer to display each of the body parts individually.

Example of the items in an Internet e-mail header that the CVM uses to identify the sender, the function, or the type of the e-mail.

The table below shows most of the fields in a typical RFC822 header.

Field	**Example**
From:	sponsorcontact@sponsor.com
To:	cvmdcu@bangate.fda.gov
Cc:	sponsorcoordinator@sponsor.com
Subject:	Email Configuration
Date:	11 May 1998 16:11:43 -0400
Importance:	Normal
Mime-Version:	1.0
Content-Type:	multipart/mixed; boundary="__NextPart__11:05:1998_(27624)"
Content-Transfer-Encoding:	7bit

When a multipart MIME message is assembled, the text will have a set of lines such as this in front of it, including the part boundary string that was specified in the header.

The example immediately below uses the ISO-8859-1 character set rather than US-ASCII, but limits the characters to 7-bit, that is octets ranging from 1-127:

__NextPart__11:05:1998_(27624)
Content-Type: text/plain; charset=iso-8859-1
Content-Transfer-Encoding: 7bit

The lines in the example below might precede an attached file called cvmform.pdf. Note that the content is identified simply as "application/octet-stream". If PDF had been defined to the originating e-mail agent, it might have been identified as "application/pdf". If PDF was defined to the receiving agent as a type that should be processed by Acrobat Reader or Exchange, the agent would launch Reader or Exchange to view the file. When the receiving agent does not recognize the Content-Type, it must treat it as "application/octet-stream", decode it, and offer the recipient the option to save it as a user file.

__NextPart__11:05:1998_(27624)
Content-Type: application/octet-stream; name=cvmform.pdf
Content-Transfer-Encoding: base64

B. E-mail Address Requirements

The e-mail address of the originating Sponsor Contact must be registered with CVM by the sponsor as outlined in Section III of this appendix. If the sender is not registered with CVM, then an electronic submission cannot be processed. The e-mail address registered with CVM must match exactly the e-mail address of the received submission.

Participating sponsors must agree to send electronic submissions to the e-CVMDCU; however, only electronic submissions should be directed to the e-CVMDCU. All other communications such as questions, comments or other information requests should be directed to the identified contact at CVM and not to the e-CVMDCU.

C. Subject Line of E-mail

The subject line is an integral part of the Center's processing of electronic information submitted via e-mail. Each electronic submission of information is identified, quality-checked, and processed based on the subject line of the e-mail message to which it is attached. The subject line for e-mail messages that contain an attached submission should be the single word identified in the guidance document specific to each type of submission. It should be only the single word, capitalized, non-quoted, and contain no special characters. Any additional information in the subject line will cause a fatal error and the submission will not be processed.

There are also several general subject lines to be used for electronic submission to CVM.

Subject Line	**Type of Electronic Submission**
REGISTER	Electronic copy of Registration Letter requesting acceptance to submit information electronically
CHANGE	Electronic notification of changes in conditions of registration
PASSWORD	Electronic request to change individual contact password

D. PDF File of Electronic Submission

For purposes of any electronic submission, the sponsor will use the appropriate format provided by CVM, which will be submitted to CVM as an encrypted Adobe® PDF file (created in Adobe Acrobat® Exchange® compatible with version 3.0)[2] attached to an e-mail message. The sponsor must either create a word processing document with the necessary data and convert it to a PDF file, or populate an Adobe Acrobat form directly.

There is to be only one PDF attachment per e-mail, and it must be no larger than 1 Megabyte (1 MB) in size. It should conform to the format and standards for the specific type of electronic submission as detailed in the guidance document. The Center's automated processing performs a quality check for number of attachments and will not process an electronic submission with more than one attachment.

Sponsors must use ISO 9660 Interchange Level 1 file naming convention, i.e., up to 8 characters (A-Z, 0-9, and _) for the file name and PDF for the file extension; an example using this convention would be filename.PDF. All incoming file attachments to the e-mail message not conforming to this naming convention will be automatically rejected by CVM processing.

E. Password Encryption and Security Measures

Each individual who submits electronic submissions will have a password consisting of 12 case-sensitive alphanumeric characters. This password will be applied to the electronic submission by the Sponsor Contact to encrypt the file before it is transmitted to CVM. Only CVM's electronic submission system and the person who submits the electronic submission will know the password and be able to open the file.

Each individual who intends to submit electronic submissions will have a unique electronic signature to verify the sender's identity. The unique electronic signature will consist of the sender's e-mail address and the password created by the sender used to encrypt the electronic submission.

[2] FDA use of specific products does not constitute an endorsement of that product

CVM will acknowledge receipt of the electronic submission by creating a new e-mail message (i.e., not by using a "Reply" feature) and sending it to the e-mail address of the individual submitting the electronic submission. The receipt will be a password-encrypted file of routing information from CVM's Submission Tracking and Reporting System (STARS) attached to an e-mail message. CVM will use the sponsor password to encrypt the file.

These requirements must be met for CVM to accept electronic submissions as the official copy, in lieu of paper, as allowed by 21 CFR 11. If sponsors are not capable of meeting these requirements, then information must be submitted in paper.

V. SECURITY MEASURES FOR ELECTRONIC SUBMISSIONS

Corporations have used the Internet as an expeditious vehicle for the exchange of information for several years. However, many corporations and government agencies have avoided using the Internet for the exchange of sensitive and/or confidential information because of concerns about security. It is important to remember that e-mail messages transmitted via the Internet have the same legal protection as regular mail sent through the U.S. Postal Service.

In developing an electronic submission project using the Internet as our message-carrying vehicle, four areas of security must be addressed adequately by all participants prior to its adoption. These areas are:

- Determine the Sponsor Disclosure/Non-Disclosure status of the information
- Authentication verification
- Determine the requirements for nonrepudiation
- Develop methods that would eliminate intentional and/or unintentional integrity problems

A. Disclosure/Non-Disclosure

Information submitted to CVM is subject to the Freedom of Information Act and FDA's regulations on public information at 21 CFR Part 20. Some information, such as trade secrets, confidential commercial and financial information is confidential in nature and is nondisclosable. CVM is not at liberty to disclose the existence of/or the information contained in INAD files, NADA applications, etc., to the general public or to other drug sponsors. Therefore, using the Internet to submit confidential information can be done only with adequate encryption. We currently recommend that this encryption be in the form of a password-protected PDF file. CVM will continue to monitor and assess the adequacy of this level of security and determine whether or not a different encryption method is necessary.

Protecting the Confidentiality of the Information in Electronic Submissions

When the PDF file is created, the Sponsor Contact submitting the electronic information will encrypt the file with his/her individual password. In Adobe Acrobat Exchange, this is done by selecting:

File ---------|
Save As ---------|
Security ----------|
Specify Password to
Open Document

Each Sponsor Contact will have an individual password that they will use to encrypt any electronic submissions. Each sponsor also provides a password to CVM that will be used to encrypt outgoing acknowledgments of receipt for submissions from that sponsor.

B. Authentication Verification

Currently, CVM receives paper submissions from sponsors via US Mail, Federal Express, UPS, etc. With these submissions, there is a cover letter on sponsor letterhead signed by an authorized sponsor official. This information allows CVM to authenticate that the submission is from the stated sponsor. Any electronic submission must also provide a means by which CVM can authenticate the origin of the electronic document.

Unique Two-Part Electronic Signature

The Registration Letter contains the name and e-mail address for each Sponsor Contact. Subsequent to the receipt of the CVM's acceptance letter, each Sponsor Contact will submit to CVM a password as described in Section III.B of this appendix. The unique combination of the e-mail address and the password will serve as the electronic signature authenticating the identity of the sender. CVM will maintain a database of the authentication signatures and will automatically reject any electronic submission received that does not match the unique combination of e-mail address and password.

Verifying the Sender's Identity

An additional precaution will be taken to ensure that the e-mail message received at CVM did indeed come from the sender designated. CVM will acknowledge receipt of the electronic submission by creating a new e-mail message (i.e., not by using a "Reply" feature) and sending it to the e-mail address of the Sponsor Contact. This e-mail message will have a PDF attachment encrypted with the sponsor provided password. If a Sponsor Contact receives an acknowledgment but has not sent an e-mail to CVM, he/she can suspect that the security of the system has been violated and should immediately report this to CVM by telephone to 301-827-8277.

C. Requirements for Nonrepudiation

Currently, time-sensitive information is submitted via certified mail so that the sponsor has a record verifying the date and name of individual who received the information at CVM. This also provides a legal basis by which drug sponsors can assert their compliance with laws and regulations.

Currently, CVM uses the date on the cover letter as the determination whether notification was as required. The sponsor will complete a date field within the PDF electronic submission file that will serve this purpose.

As a means of verifying that the information was received, CVM should acknowledge receipt with an e-mail message back to the sponsor within two business days of its receipt.

Verifying Receipt of Electronic Submissions

The acknowledgment of receipt will be an e-mail message with an attached encrypted PDF file containing logging information from CVM's STARS system. CVM will use the sponsor password to encrypt this file before sending the acknowledgment to the Sponsor Contact. The subject line of the e-mail message will be blank.

If the Sponsor Contact has not received an acknowledgment by the third business day after sending in the electronic submission, the Sponsor Contact should call CVM at 301-827-8277 to determine the fate of the transmission.

D. Submission Integrity

Currently, the integrity of the accuracy and veracity of the content of a submission to CVM is the responsibility of the sponsor. If sections of a paper submission are missing or illegible, CVM requires the sponsor to provide copies of the missing or illegible information. Though remote, a possibility exists that intentional or unintentional changes could occur to an electronic submission that would probably not happen to a paper submission. For example, unintentional "scrambling" of the submission may occur during transmission so that CVM receives a corrupted, non-usable file. Further, an example of an intentional change would be if a message were intercepted en route, changes made to the content and then the message sent on as if from the original sender.

CVM will rely on the password encryption of the PDF file to ensure the integrity of the electronic submission. If the file is received by CVM intact and can be decrypted and opened by Adobe Acrobat Exchange, then CVM will assume no changes occurred to the submission once it was e-mailed from the sponsor.

VI. CHECKLIST FOR ELECTRONIC SUBMISSIONS

In order to participate in any electronic submission project, sponsors must:

- have MIME (base64) compliant access to the Internet. See Section IV.A of this appendix for details.
- use the appropriate form or format provided by the CVM.
- conform to an ISO 9660 Interchange Level 1 compatible naming convention for PDF files e-mailed to the CVM. The name of the attached file must be 8 characters or less with the letters PDF as an extension, i.e., xxxxxxxx.PDF. See Section IV.D of this appendix for details.
- register with the CVM to participate.

REGISTRATION PROCESS (See Section III of this appendix for details.):

1. Send a single, original, signed Registration Letter via US mail to CVM. See Section III.A. for an example of the Registration Letter. The letter should contain:
   a) name, mailing address, phone number, and e-mail address of the Sponsor Project Coordinator;
   b) names, mailing addresses, phone numbers, and e-mail addresses for each Sponsor Contact who will be submitting electronic submissions;
   c) a 12 alphanumeric character password that is case sensitive. This password must be changed at regular interval. See Section III.B of this appendix for details;
   d) the subject of letter will be **Registration Letter for Electronic Submission to CVM** to clearly identify the purpose of the letter.
2. Create a PDF copy of the Registration Letter. Encrypt the PDF file with the sponsor password, attach it to an e-mail message, and send it to cvmdcu@bangate.fda.gov. The subject line of the e-mail message must be the word **REGISTER**.
3. Await an e-mail message from the CVM. CVM will send this message to the Sponsor Project Coordinator named in the registration letter. The message will have a encrypted PDF file attached containing an acknowledgment of receipt of the Registration Letter. The password necessary to decrypt the PDF file receipt will be the sponsor password sent in the Registration Letter. A paper response will also be sent. If you have not received both of these acknowledgments within one month, notify CVM by calling 301-827-8277.
4. Each Sponsor Project Coordinator and Sponsor Contact must send an individual, 12 character case sensitive password to cvmdcu@bangate.fda.gov. This password is contained in a PDF file attachment which has been encrypted using the sponsor password. Subject line of the e-mail message is **PASSWORD**. Passwords must be changed at regular interval. See Section III.B of this appendix for details.
5. Await an acknowledgment receipt via e-mail from CVM (stars@bangate.fda.gov) before using the new password.